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Research paper

A formulation of grape seed, Indian gooseberry, turmeric and fenugreek helps controlling type 2 diabetes mellitus in advanced-stage patients

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ABSTRACT

Introduction: The aim of this clinical study was to determine whether an add-on treatment with a herbal product (Plantabetics®) containing extracts of grape seed, Indian gooseberry, turmeric and fenugreek seeds, improved glycemic control in advanced-stage patients, who were no longer responding to a combination therapy of metformin and sulfonylurea.
Methods: This was an open label, single arm before/after study of 84 days duration. A total of 50 patients with type 2 diabetes, who were on a stable dose of metformin and sulfonylurea but not showing any improvement in diabetic control, were recruited. Patients were not taking any other herbal supplements or medication. They were instructed to take one capsule of the investigational product two times daily along with their diabetes medication. End points were glycated hemoglobin (HbA1c), fasting blood sugar, and postprandial blood sugar. Safety parameters were also evaluated.
Results: Treatment with the investigated herbal product in conjunction with prescribed diabetes medication resulted in a > 1% unit reduction in average glycated hemoglobin value (from 8.8%/73 mmol/mol to 7.5%/58 mmol/mol; $p < 0.001$) as well as significant reduction in average fasting (from 8.8 mmol/l to 6.6 mmol/l; $p < 0.001$) and post prandial blood sugar values (14.6 mmol/l to 10.4 mmol/l; $p < 0.001$) in the majority of the study population. The herbal product was moreover well-tolerated and safe to use.
Conclusions: The investigated product in combination with oral hypoglycemic agents is a promising candidate for regaining glycemic control in advanced-stage type 2 diabetes patients.

1. Introduction

Type 2 diabetes mellitus is a multiple metabolic disorder, including disorder of sugar and fat metabolisms, disorder of endogenous enzyme production and disorder of endocrine function [1,2]. It is manifested by high blood sugar values, resulting in a significantly increased risk of developing microvasculoar (e.g. retinopathy, nephropathy) as well as macrovascular (e.g. stroke, ischemia of heart and lower extremities) complications and increased mortality compared to the population without diabetes. Therefore, the current therapeutic approach for type 2 diabetes targets the sugar metabolism disorder. Indeed, several large studies have shown that reduction of glycated hemoglobin, a marker for the long-term blood glucose level, of just 1% unit (11 mmol) significantly reduces the risk for type 2 diabetes-associated microvascular diseases [3,4]. Glycemic control is initially achieved by oral hypoglycemic agents (OHAs) [5]. Most widely used OHAs are metformin and sulfonylureas. OHAs show good effect in the early stages of type 2 diabetes. However, the disease is of a progressive nature and it becomes increasingly difficult to achieve the targeted glycemic control with OHAs and insulin injection becomes necessary [6]. Progressive reduction in β-cell mass and deregulation of insulin promoter due to chronic exposure to high glucose concentrations are the main reasons for uncontrolled diabetes in later stages [7,8]. The latter effect termed as 'glucose toxicity' is still reversible. The more detrimental effect of prolonged elevated blood glucose concentrations is the formation of reactive oxygen species, e.g. through glucose autoxidation or oxidative phosphorylation. The antioxidative defense system of pancreatic β-cells is particularly weak due to low levels of endogenous antioxidants and can be imbalanced by overproduction of free radicals in hyperglycemic condition [8,9]. The resulting oxidative stress causes irreversible damage to β-cells and eventually leads to apoptosis [1,8,10,11]. Pancreatic islet has the ability to generate new β-cells. However, in later stages of type

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2 diabetes, a high rate of β-cell apoptosis and interleukin 1β-mediated inflammation in pancreatic islets may prevent generation of new β-cells whereas prevailing oxidative stress prevents their survival [12]. With reduction in β-cell mass, less and less insulin is available to the organism with time. Consequently, OHAs, which act either by increasing insulin release from β-cells or increasing insulin sensitivity of receptors can no more be effective. Apart from hyperglycemia and oxidative stress, hyperlipidemia is also responsible for β-cell apoptosis [12]. It has been reported that β-cell apoptosis and/or necrosis may activate specific immunological phenomena [12,13]. Hence, immune modulatory agents might play a positive role in management of type 2 diabetes. Taken together, high oxidative stress, resulting inflammatory processes, hyperlipidemia and attenuation of immune function have to be specifically targeted in addition to glycemic control for restricting the progression of diabetes and for better diabetes management.

This situation presents an unmet medical need for developing more efficacious and safe treatment options with long-term and better glycemic control for diabetes. In this regard, herbal interventions present a promising option since many of them have anti-diabetic properties [14,15]. Polyherbal formulations have been found to be effective against diabetes in a number of studies [16–18]. All of these studies used phytotherapy as the sole treatment and included one or more herbal blood sugar lowering agents that act like OHAs or insulin, e.g. *Mormordica charantia, Gymnema sylvestre* [16–18]. Conventional OHAs, in spite of their side effects, have a long history of successful usage and doctors as well as patients rely on them heavily. Therefore, we developed a quality-controlled polyherbal formulation, "Plantabetics", as an add-on therapy. For this purpose, our formulation does not contain direct blood sugar lowering ingredients. This has the benefit that people with type 2 diabetes can continue with their prescribed medication and additionally take Plantabetics as an adequate complementary therapy.

The final product (Plantabetics®) was composed of 350 mg standardized extracts of fenugreek (*Trigonella foenum-graecum)*, Indian gooseberry (*Emblica officinalis*), grape seed (*Vitis vinifera*) and turmeric (*Curcuma longa*) filled in a cellulose capsule. These ingredients were specifically chosen to target oxidative stress, inflammation and immune dysfunctions in type 2 diabetes mellitus. Tannins of Indian gooseberry and proanthocyanidins of grape seeds have been reported to induce endogenous antioxidant enzyme production and improve antioxidant status in rat's brain and heart [19,20]. Polyphenols of turmeric have antioxidant as well as anti-inflammatory properties [21,22]. Besides its effects on hyperlipidemia, Fenugreek contains immune regulatory polysaccharides [23,24]. It has been established that immune imbalance can also be a cause of β-cell death in type 2 diabetes, like in case of type 1 [12,25]. In order to determine the effect of the above product on blood sugar control we conducted an open label clinical study with type 2 diabetes patients in advanced stage where OHAs did no longer achieve sufficient glycemic control.

To our knowledge this is the first report of a clinical before/after study with a quality-controlled herbal formulation devoid of hypoglycemic agents specifically designed as an add-on therapy to target metabolic disorders of type 2 diabetes mellitus, which are not adequately addressed in conventional therapy.

2. Research design and methods

2.1. Product composition

The investigational Product (IP) contained 350 mg total extracts of fenugreek (*Trigonella foenum-graecum,* 110 mg), Indian gooseberry (*Emblica officinalis,* 90 mg), turmeric (*Curcuma longa,* 70 mg) and grape seed (*Vitis vinifera,* 80 mg) in the form of capsules. The product is available under the trade name Plantabetics® in Germany and Europe and is registered as a "food for special medical purpose – a partial balanced diet for dietary management of type 2 diabetes mellitus" as per Commission Directive 1999/21/EC .

2.2. Quality control

Herbal products show geographical and seasonal variations in constituents and need proper quality control for maintaining standard and efficacy. Analytical quality control according to GMP is very difficult in polyherbal formulations containing more than 4 or maximum 5 plants. Therefore, the product was limited to 4 plant extracts. Methods for quality control were developed by using a suitable marker substance for each individual ingredient like curcumin for *Curcuma longa* and elagic acid for *Emblica officinalis*.

2.3. Clinical study

2.3.1. Study design

The study was designed as a prospective, single arm, open label investigation of the efficacy and safety of the IP in patients with type 2 diabetes not responding to a therapy of metformin and sulfonylurea, which is usually given in advanced stage. Study duration was 84 days. The study was conducted in India under full GCP compliance at 3 sites. The trial was registered in national trial register according to WHO instruction under the following clinical trial number: CTRI/2011/11/002170; clinical trials registry India (http://www.who.int/ictrp/network/ctri2/en/).

A local clinical research organization, Vedic Lifesciences Pvt. Ltd. (Mumbai), was contracted for clinical research service and implementation of GCP guidelines

2.3.2. Ethical procedure

This study was conducted according to International Conference on Harmonization Good Clinical Practices (ICH-GCP), applicable government regulations and institutional research policies and procedures. The study protocol, informed consent form (ICF) and other required documents were submitted to an independent ethics committee (IEC-Aditya of Ahmadabad, India) and written approval for each study site was granted. The study was conducted throughout under vigilance of IEC. Prospective participants were provided an approved ICF in English and other local languages describing the main feature of the study according to GCP guidelines. Doctors explained the study to them providing sufficient information to make an informed decision about their participation in this study. Patients or patient's legally acceptable representative provided signed and dated informed consent for study participation.

2.3.3. Investigators

The following doctors in Mumbai, India, were responsible for patient recruitment, selection and implementation of the study according to protocol. The patients were recruited in the respective clinics mentioned below.

1. Rajesh Kewalramani, MBSS, Shanti Niketan, Shop No-16, Bldg. No.13-A, Kandarpada, Dahisar (West), Mumbai-400 068, Maharashtra, India.
2. Shrikanta Pensalwar, MBSS, Balaji Clinic, Main Devipada Road, Borivali (East), Mumbai-400 066Maharashtra, India.
3. Sanjay Palimkar, MBSS, Shree Siddhi Clinic, Shop no. 01, H.S Khan Chawl, S. N. Dube road, Rawalpada, Dahisar (E), Mumbai. 400 068, Maharashtra, India.

2.3.4. Patients

2.3.4.1. Inclusion criteria. For participation in the study, patients were required to fulfill following inclusion criteria:

1. Age: 30–60 years
2. Diagnosed with non insulin dependent type 2 diabetes and under treatment for at least one year
3. On a stable dose of metformin and sulphonylurea for at least 3 months before recruitment without showing any improvement in blood sugar parameters
4. HbA1c $\geq$ 7.5% but $\leq$ 10% for the previous 3 months or more, tendency upwards
5. Patients who had been following a steady lifestyle (in terms of diet and exercise) for the last 3 months and were willing to continue the same without any changes during the study period
6. Patients who were on hypolipidaemic drugs (e.g. statins) for lowering blood lipid levels, were required to be on a stable dose of these drugs for at least 3 months before recruitment

2.3.4.2. Exclusion criteria. Patients fulfilling any of the following exclusion criteria were ineligible for participation in the study:

1. Patients receiving the following medications
   a) Herbal product for any condition
   b) Any other OHA besides Metformin and Sulfonylurea
   c) Insulin
   d) Any drug (besides that prescribed for glycemic control) that is known to affect blood sugar levels
2. Heavy alcohol drinkers
3. Hepatic impairment (as evidenced by serum glutamate pyruvic acid > 1.5 times the upper limit of normal)
4. Presence of major systemic disorders
5. Known cases of renal impairment or cardiac disorders
6. Women who were pregnant/lactating/unwilling to adopt suitable method of contraception during the study period and up till 3 months after study completion

2.3.4.3. Withdrawal criteria. Patients were withdrawn from the study under the following conditions:

1. Earnest request of the patient assigning a reason for withdrawal
2. Discretion of the investigator
3. FBS and PPBS values increase by 20 mg/dl (1.1 mmol/l) from baseline values on 2 consecutive visits
4. Any abnormality in the laboratory or clinical parameters depending upon the severity and seriousness of the condition
5. Serious adverse events where continuation of study posed serious risks to the patients
6. Patients consumed any other medicines for lowering blood sugar and/or blood lipid levels
7. Patients who did not get their laboratory testing done within 7 days of end of treatment visit (EoT) i.e. day 84
8. Patients had an IP compliance of $\leq$80% at any visit
9. Patients did not come within 7 days of his/her scheduled follow-up visit
10. Patients became pregnant during the course of the study
11. Any single major protocol deviation occurring more than once during the study

2.3.4.4. Lost to follow up. Patients were considered as lost to follow up if they could not be contacted during the study period.

2.3.4.5. Protocol deviation. Patients were expected to comply with the requirements of the protocol. Any deviation from the study methodology was considered a deviation and was recorded in the case report form.

Following were considered as major protocol deviations:

- Patients with an IP compliance of $\leq$90% at any visit
- Patients who did not come for the follow-up visit within $\pm$2 days but came within $\pm$7 days of the scheduled visit.

NOTE: Patients were withdrawn from the study if any of the above deviations occurred more than once during the study.

2.3.5. Medication plan

The IP was dispensed on Day 0, 21, 42 & 63. Patients were asked to take 2 capsules daily, one capsule of IP each morning and evening before meals with enough water along with their prescribed medication(s). Patients received 50 capsules of the IP packed in plastic bottles on each visit and returned the unused number of capsules to account for regular consumption.

2.3.6. Study endpoint

The primary efficacy endpoint was the effect of IP on glycated hemoglobin (HbA1C) as compared with baseline. Secondary efficacy endpoints were the effect of IP on fasting blood sugar (FBS), postprandial blood sugar (PPBS), plasma triglyceride, HDL and LDL values as compared with baseline. Assessment of FBS and body mass index was done on all visits (Day 0, 21, 42, 63 & 84). Assessment of HbA1c, PPBS and lipid profile was done on alternate visits (Day 0, Day 42 & Day 84). Check of IP compliance was conducted on all the visits.

2.3.7. Safety parameters

In addition, safety parameters were investigated in order to assess the safety of IP. The following parameters were checked for the assessment of safety:

1. Vital Parameters:
   a) Pulse rate
   b) Respiratory rate
   c) Systolic and diastolic blood pressure
2. Systemic Examination:
   a) Monitoring of adverse effects and serious adverse effects
3. Blood and Urine Tests:
   a) SGPT (serum glutamic pyruvic transaminase)
   b) routine Urine:
      (1) Macroscopic analysis: color, clarity, odor, specific gravity, pH, protein (nephritis), glucose, ketone, bile salts, bile pigments, urobilinogen, nitrites, leukocyte esterase (WBC esterase),
      (2) Microscopic analysis: red blood cells, white blood cells, casts, crystals, bacteria, yeast cells, parasites, squamous cells.

Safety parameters were checked on all visits.

2.3.8. Blood sampling and measurements

The participating physicians and their assistants carried out blood sampling. Patients were instructed to visit their clinic on scheduled days in the morning in fasting condition for blood sample collection so that the time interval between last dose of Plantabetics and blood sampling was at least 10 h. Samples were

frozen and transferred to certified pathological laboratories, where they were kept in refrigerators until analysis.

2.3.9. Statistical methods

Statistical Analysis was done by Vedic Lifesciences Pvt. Ltd. (Mumbai). Statistical analysis of safety variables and vital parameters was performed on a group of 48 subjects (intention-to-treat analysis) using paired *t*-test. The analysis of efficacy variables was carried out on a group of 35 subjects (per protocol analysis) using paired *t*-test. The study population of 35 was further divided into 2 groups: responders and non-responders based on reduction in HbA1c from baseline to end of treatment.

3. Results

3.1. Patient recruitment

Doctors at 3 sites in Mumbai, India recruited patients. From a total of 82 patients, 50 were considered for the study. Fig. 1 shows the patient recruitment and selection process. The demographic and other baseline characteristics of the 50 recruits are shown in Table 1. 42 patients completed the study; however, only 35 of these satisfied all criteria of the study protocol (Fig. 1).

3.2. Measurement of treatment compliance

First, an analysis of treatment compliance was conducted on a study population of 35 by counting the number of unused capsules after each visit, i.e. on day 21; 42; 63 and 84. The mean treatment compliance per 21-day interval was > 98%, which was deemed acceptable.

3.3. Safety evaluation

Safety evaluation was conducted on a study population of 48 patients with an intention-to-treat analysis. Two patients who did not receive a single dose of IP and discontinued the study on day 0 were excluded from analysis (1 withdrawal and 1 lost-to-follow-up). No statistically significant changes were observed in pulse rate, blood pressure and respiratory rate, SGPT and urine analysis values from baseline to end of treatment (EoT). A total of 5 adverse effects were reported in 5 patients, all of which were of mild to moderate intensity and were resolved during the study. Hypoglycemia of moderate intensity was reported in 1 patient, which was probably related to the study drug. Other adverse effects were hyperacidity, conjunctivitis, swelling of legs and headache; all of which were mild in intensity and unrelated to the study drug. In summary, the investigated herbal mixture was shown to be safe.

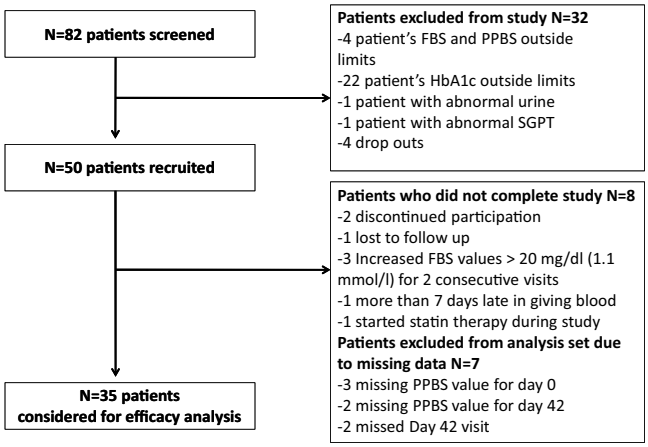

Fig. 1. Patient recruitment and selection process. This diagram depicts the patient recruitment and selection process according to study protocol.

Table 1
Baseline characteristics (N = 50).

Age (SD)	50.62 (7.48)
Sex	
Male N (%)	30 (60)
Female N (%)	20 (40)
Pre-existing condition	
Hyperlipidemic N (%)	5 (10)
Hypertension N (%)	20 (40)
Cardiovascular disease N (%)	1 (2)
Thyroid N (%)	3 (6)
FBS mmol/l (SD)	9.32 (2.78), note: N = 47 at baseline
PPBS mmol/l (SD)	15.22 (4.22)
HbA1c% (SD)/mmol/mol (SD)	8.86 (1.14)/73 (12.5)
HDL mmol/l (SD)	1.2 (0.33)
LDL mmol/l (SD)	3.08 (1.00)
Serum cholesterol mmol/l (SD)	5.08 (1.18)
Serum triglyceride mmol/l (SD)	1.81 (0.97)
BMI (SD)	27.14 (4.15)

Abbreviations: N, number of patients; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; PPBS, post prandial blood sugar; SD, standard deviation.

3.4. Efficacy

3.4.1. Analysis set used for efficacy analysis

Efficacy evaluation was conducted on a study population of 35. Three recruited patients did not complete the study due to self-withdrawal and lost-to-follow-up (Fig. 1). Five patients were discontinued from the study based on the withdrawal criteria (see materials and methods). Additionally, 7 patients were excluded from the analysis set due to missing data for day 0 or day 42 (Fig. 1).

3.4.2. Analysis of efficacy

Mean changes in efficacy parameters from the baseline to EoT are presented in Table 2. A statistically significant reduction in HbA1c was observed from baseline to EoT ($p = 0.04$). A notable reduction was observed in FBS and PPBS from baseline to EoT but was not statistically significant ($p \geq 0.05$). A similar notable reduction without statistical significance was also observed from baseline to EoT in the serum triglyceride.

It was noticed that although the majority of subjects (65.71%) showed a reduction in HbA1c the remainder did not show any effect or displayed even an increase in HbA1c (data not shown). Therefore, we conducted a subgroup analysis for efficacy

Table 2
Analysis of mean changes in efficacy parameters from baseline to EoT (N = 35).

Parameters	Baseline (SD)	EoT (SD)	P value
HbA1c%/mmol/mol	8.70 (0.87)/72 (9.5)	8.13 (1.39)/65 (15.2)	0.04
FBS mmol/l	9.19 (1.92)	8.15 (2.78)	0.07
PPBS mmol/l	15.45 (4.19)	13.40 (5.68)	0.09
HDL mmol/l	1.19 (0.32)	1.08 (0.34)	0.18
LDL mmol/l	3.03 (1.1)	3.29 (0.9)	0.29
Serum cholesterol mmol/l	5.02 (1.3)	5.09 (1.2)	0.82
Serum Triglycerides mmol/l	1.87 (1.1)	1.63 (0.79)	0.31
BMI Kg/m^2	26.78 (4.22)	26.59 (3.98)	0.84

Abbreviations: EoT, end of treatment; N, number of patients; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; PPBS, post prandial blood sugar; SD, standard deviation.

Table 3
Analysis of mean changes in efficacy parameters in subgroups from baseline to EoT (N = 35).

Parameters	Responders (N = 23)			Non responders (N = 12)		
	Baseline (SD)	EoT (SD)	p	Baseline (SD)	EoT (SD)	p
HbA1c%/mmol/mol	8.76 (0.82)/73 (9.0)	7.50 (0.94)/58 (10.3)	$p < 0.001$	8.60 (0.98)/70 (10.7)	9.33 (1.35)/78 (14.8)	0.004
FBS mmol/l	8.80 (1.56)	6.95 (1.97)	$p < 0.001$	9.92 (2.38)	10.44 (2.16)	0.62
PPBS mmol/l	14.58 (3.03)	10.46 (4.13)	$p < 0.001$	15.85 (5.01)	15.46 (3.91)	0.83
HDL mmol/l	1.17 (0.31)	1.05 (0.26)	0.14	1.21 (0.35)	1.14 (0.46)	0.67
LDL mmol/l	2.82 (1.1)	3.04 (0.84)	0.46	3.43 (1.02)	3.77 (0.85)	0.39
Serum cholesterol mmol/l	4.81 (1.31)	4.73 (0.96)	0.81	5.42 (1.25)	5.77 (1.37)	0.52
Serum Triglycerides mmol/l	1.86 (1.05)	1.54 (0.88)	0.28	1.89 (1.24)	1.81 (0.55)	0.84
BMI kg/m^2	26.98 (4.91)	26.82 (4.67)	0.91	26.41 (2.55)	26.15 (2.24)	0.80

Abbreviations: EoT, end of treatment; N, number of patients; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; PPBS, post prandial blood sugar; SD, standard deviation.

evaluation. The study population was divided into 2 subgroups: 'responders' and 'non-responders'. Responders were defined as patients who showed at least a reduction of $\geq 0.1\%$ (1.1 mmol/mol) in HbA1c from baseline to EoT and patients who did not meet this threshold of HbA1c reduction were defined as non-responders. Out of 35 patients in the study population, 23 (65.71%) were responders and 12 (34.29%) were non-responders (Table 3). In the responder subgroup, there was a statistically significant reduction from baseline to EoT in HbA1c (14.58%), PPBS (28.25%) and FBS (21%) with $p < 0.001$ (Table 3). Figs. 2–4 show the mean reduction in HbA1c, PPBS and FBS in the responder group during treatment. Fig. 5 shows the change in HbA1c from baseline to EoT in all 35 patients as a waterfall plot. Four patients had an increased HbA1c of more than 1% unit at EoT (Fig. 5). Eleven patients showed an HbA1c reduction of more than 1% unit, some even more than 2% units (Fig. 5). A reduction was observed from baseline to EoT, in the levels of serum triglycerides and cholesterol, though this reduction was not statistically significant ($p \geq 0.05$). In the non-responder subgroup, a statistically significant increase of HbA1c was observed at EoT ($p = 0.004$) (Table 3 and Fig. 2). No statistically significant changes in FBS, PPBS, serum cholesterol and triglycerides were observed within this subgroup ($p \geq 0.05$) (Table 3 and Figs. 3 and 4).

4. Discussion

This open label before/after study was conducted to investigate the safety and efficacy of the herbal formulation Plantabetics®. The investigational product (IP) is composed of edible plant extracts containing natural compounds capable of inducing endogenous antioxidant enzymes and with immunomodulatory, hypolipidemic and anti-inflammatory activities [19–25]. The product is intended as a complementary remedy for people with type 2 diabetes in advanced stage, i.e. it is to be used in conjunction with prescribed blood sugar lowering diabetes medication.

The study focused on advanced-stage diabetes patients with poor glycemic control and not responsive to standard medication. Elevated FBS and glycated hemoglobin values ($7.5\% \leq \text{HbA1c} \leq 10\%$) with an increasing trend according to blood reports prior to intervention and at the time of inclusion indicated poor glycemic control in the recruited subjects. The use of the IP in the study population showed evidence of efficacy, safety and tolerability. Notably the product restored blood sugar control in the majority of the advanced type 2 diabetes patients, defined as "responders" (Table 3). In the responder group, mean PPBS was significantly reduced (28.25%) from 14.58 mmol/l at baseline to 10.46 mmol/l at EoT (Table 3). Parkin and Brooks assessed the importance of PPBS-

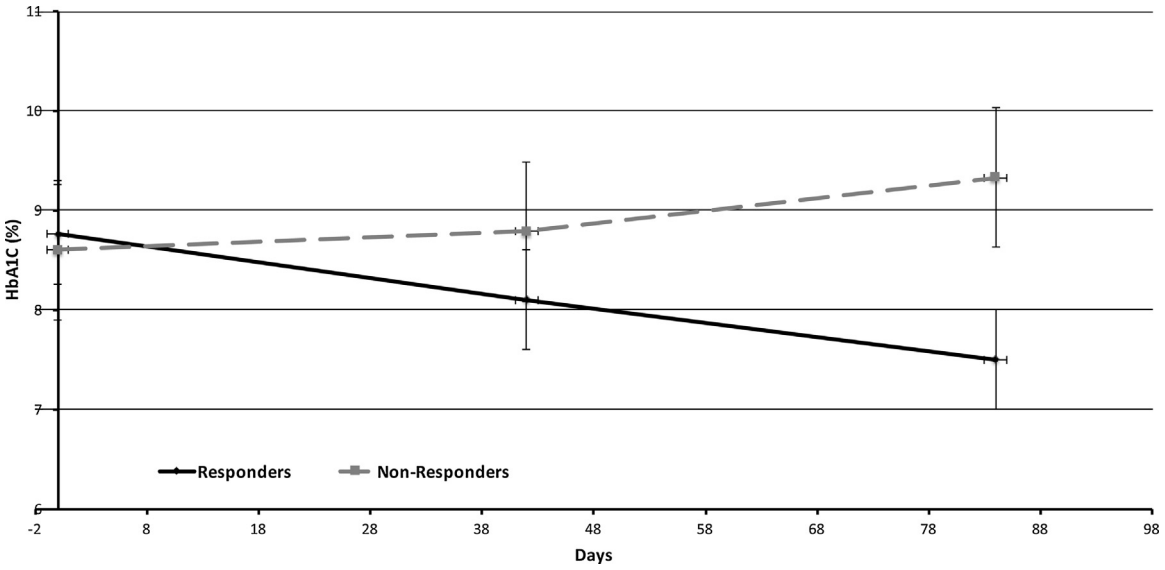

Fig. 2. Change in HbA1c in responders and non-responders during treatment. This graph shows the mean change in HbA1c in the two sub-groups during treatment with the investigational product. Solid black line: responders; dotted grey line: non-responders.

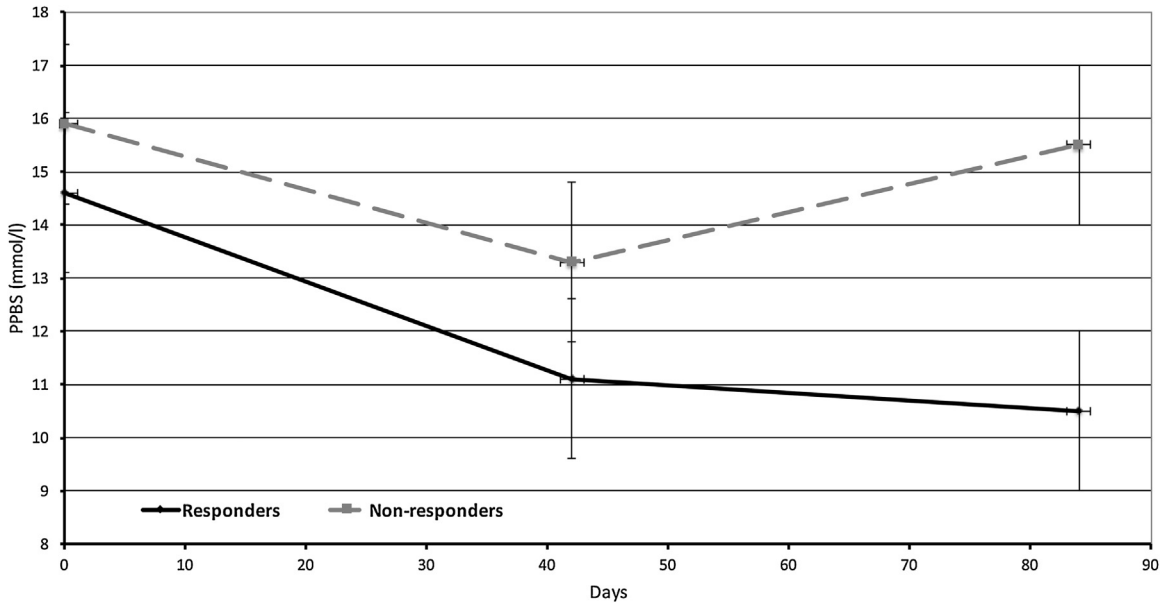

Fig. 3. Change in PPBS in responders and non-responders during treatment. This graph shows the mean change in PPBS in the two sub-groups during treatment with the investigational product. Solid black line: responders; dotted grey line: non-responders.

control in diabetes patients and came to the conclusion that it is an important indicator for overall glycemic control [26]. In the responder subgroup, a mean 1.26% unit (15 mmol/mol) reduction in glycated hemoglobin (HbA1c) was observed within three months (Table 3). Several patients of the responder group even showed a reduction of 2% unit (22 mmol/mol) in HbA1c (Fig. 5). Several large randomized trials demonstrated that per 1% unit reduction in glycated hemoglobin a 30–35% reduction in micro-vascular complications was achieved [27–29]. Moreover, the mean HbA1c in the responder group of 58 mmol/mol (7.5% unit) is close to the goal of <53 mmol/mol (7.0% unit) of the American Diabetes Association (ADA) [30]. Mean fasting blood sugar was 6.95 mmol/l at EoT being within the ADA target range of 4.6–7.2 mmol/l (Table 3 and Fig. 4). These results indicate that the study drug as an add-on therapy significantly improves the control of blood sugar in the majority of advanced-stage type 2 diabetes patients. One patient suffered from hypoglycemia and consulted the investigating physician, who reduced the dose of sulphonylurea to stabilize the condition (data not shown). The FBS values of several patients came down below 5 mmol/l during the study period (data not shown). In the longer run, these patients may need a reduction in their diabetes medication in order to avoid a hypoglycemic episode.

A similar before/after study using a formulation containing ten plants (including *Curcuma longa* and *Emblica officinalis*) as the sole treatment showed a significant reduction of blood glucose and

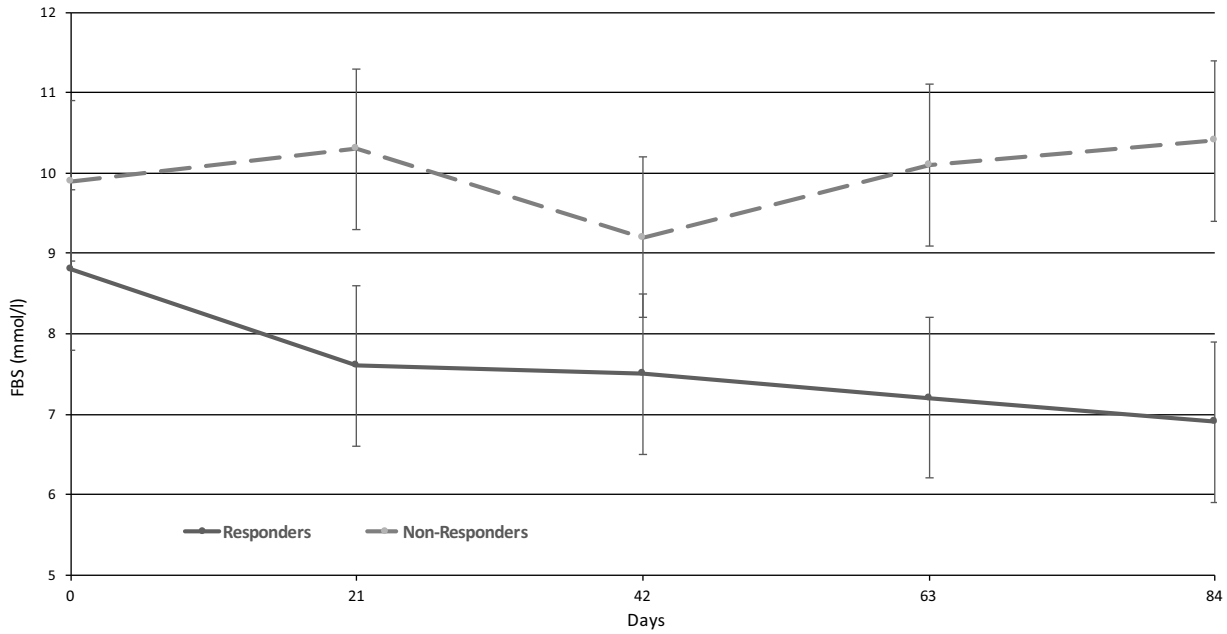

Fig. 4. Change in FBS in responders and non-responders during treatment. This graph shows the mean change in FBS in the two sub-groups during treatment with the investigational product. Solid black line: responders; dotted grey line: non-responders.

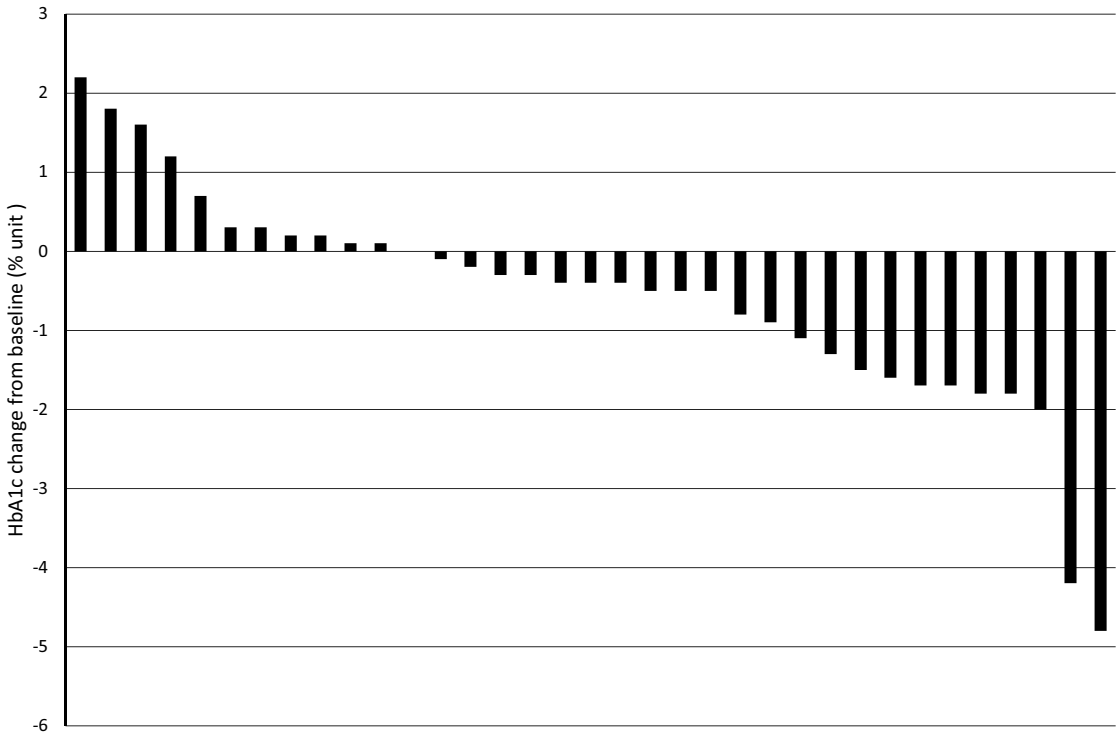

Fig. 5. Change in HbA1c from baseline at end of treatment for all patients. This waterfall plot depicts the change in HbA1c (% unit) from baseline at EoT for individual patients.

glycosylated hemoglobin levels within six months of daily adminsitration in type 2 diabetes patients [18]. Additionally, significant improvement of antioxidant enzyme activities was noted [18]. A recent review by Ghorbani assessed the results of studies on treatment of diabetes with polyherbal formulations in animal models as well as a small number of clinical trials [31]. Many of these formulations showed better efficacy than the reference drugs in pre-clinical studies. *Mormordica charantia*, *Gymnema sylvestre*, *Syzgium cumini (synonym Eugenia Jambola)*, *Trigonella foenum-graecum* and *Curcuma longa* were the most commonly used plants in those polyherbal anti-diabetic formulations. The first three plants are well known blood sugar lowering agents and are frequently used in ayurvedic anti-diabetic formulations as natural counterparts of synthetic OHAs or insulin [32–34]. Besides a long history of traditional use *Trigonella foenum-graecum*, *Curcuma longa* and *Emblica officinalis* have been thoroughly investigated and are well evaluated botanicals in terms of efficacy and safety in treatment of diabetes [35–38]. Recently, grape seed extract has been the subject of many pre-clinical and clinical studies and was found to be very effective in treatment of diabetes associated metabolic disorders [39–41]. Thus, traditional use and recent scientific findings both substantiate the plausibility of using these four extracts in our formulation as active and safe ingredients and corroborate the findings of this study.

This clinical study also showed that a minority of type 2 diabetes patients in advanced stage did not benefit from the IP. This group was defined as non-responders. The group of responders in this study was nearly twice as large as the non-responders (23 vs. 12). The non-responders showed a mean increase of HbA1c of 8 mmol/mol (0.73% unit) at EoT (Table 3). No significant changes in the other parameters were observed. As patients were instructed to take IP along with OHAs, a possible explanation for the elevated HbA1c in some patients of the non-responder group may be the inhibition of drug uptake transporters by IP constituents like tannins and flavonoids leading to decreased bioavailability of metformin as demonstrated by Mandery et al. [42]. Likewise, in his review of pharmacological and clinical studies on the effect of cinnamon on glycemic control Medagamma found that when cinnamon, which also contains tannins, was used in conjunction with metformin its glucose-lowering effect was masked by metformin [43].

We conclude that a time gap of at least 2 h must be maintained between IP and any other medication, including OHAs, in order to avoid possible drug interactions.

4.1. Strength and limitations of the work

Insulin therapy is the last choice of treatment for advanced-stage type 2 diabetes patients when a point of therapy saturation is reached and patients do not respond to conventional OHAs anymore. This study demonstrated for the first time that glycemic control can be revived in such patients by using our polyherbal formulation as an add-on therapy to conventional OHAs. Another strength of this study is that by limiting the number of herbal ingredients a proper quality control of this product could be established, which is essential for ensuring consistent efficacy.

This work has certain limitations. It is a single-arm study without a control group. Since this study involved people with uncontrolled type 2 diabetes, a placebo control group might pose a too high risk for the subjects. Therefore, the inclusion of an active-controlled group would improve the study and help to establish a reference for the efficacy. Parameters reflecting the presumed mode of action, e.g. serum insulin level and antioxidant markers, are lacking.

5. Conclusion

This study has elicited useful evidence that the investigated herbal product is effective in achieving glycemic control in

advanced stages of type 2 diabetes with poor response to OHAs alone. The mode of action of the IP is presumably by lowering pancreatic oxidative stress, inflammation and modulating immune response in order to prevent β cell apoptosis and facilitate cell replication [19–25,31–41].

In conclusion, the long-term use of the investigated herbal product (Plantabetics®) in conjunction with prescribed medication may help achieving better diabetes management and may significantly reduce diabetes-associated complications. The product may also be suitable as a preventive measure for pre-diabetes patients and in high-risk populations since no directly blood sugar lowering agent is included in the formulation.

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Role of the funding source

The owner of the funding source (Plantachem GbR) has developed the product and financed the clinical study.

Conflicts of interest

We wish to state the following potential conflicts of interest: Dr. Shanta Banerjee has developed the investigated herbal product (Plantabetics®) and is CEO of the company owning and marketing the product (Phytomed Service UG, Seegefelder Weg 425, 13591, Berlin, Germany). Sangeeta Banerji receives her salary from Phytomed Service UG, Seegefelder Weg 425, 13591, Berlin, Germany.

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